Early Detection Research Network

Manual of Operations

Revision History

Version	Date	Change
1	01-11-01	Created Sections 1, 2, 3, 4, 5, 6 and Appendices I, II, III
1.1	07-19-01	Created Appendix IV
	10-01-01	Created Revision History page; Edited Sections 6.2.6 and 6.2.7
1.2	05-02-02	Revised sections 2.2.1, 3.1, 3.1.1, 4.1, and updated Appendices II and III
	02-24-03	Revised section 6.1
	02-25-03	Revised Appendix III

Table of Contents - EDRN Manual of Operations

SECTION 1 ORGANIZATION AND DEVELOPMENT

The Division of Cancer Prevention in the National Cancer Institute created the Early Detection Research Network (EDRN) for supporting investigator-initiated, collaborative research on molecular, genetic and other biomarkers for cancer detection and risk assessment. A number of programmatic review groups at NCI recommended that the EDRN be created.

Funded through peer-reviewed Cooperative Agreements, the EDRN has four components – Biomarkers Developmental Laboratories (BDL), Biomarkers Validation Laboratories (BVL), Clinical/Epidemiologic Centers (CEC) and the Data Management and Coordinating Center (DMCC). Each component was reviewed and funded separately. The BDLs are responsible for the development and characterization of new or refinement of existing biomarkers. The BVLs serve as a Network resource for clinical and laboratory validation of biomarkers that include technological development, refinement and quality control. The CECs conduct clinical and epidemiological research regarding the clinical application of biomarkers. The DMCC is responsible for coordinating the EDRN research activities, providing logistic support for meetings, and conducting statistical and biocomputational research. The network is governed by the Steering Committee, consisting of the Principal Investigators of the EDRN and NCI staff. The Network also has a Network Consulting Committee composed of non-EDRN investigators appointed by NCI to review the progress of the Network and to recommend new research opportunities.

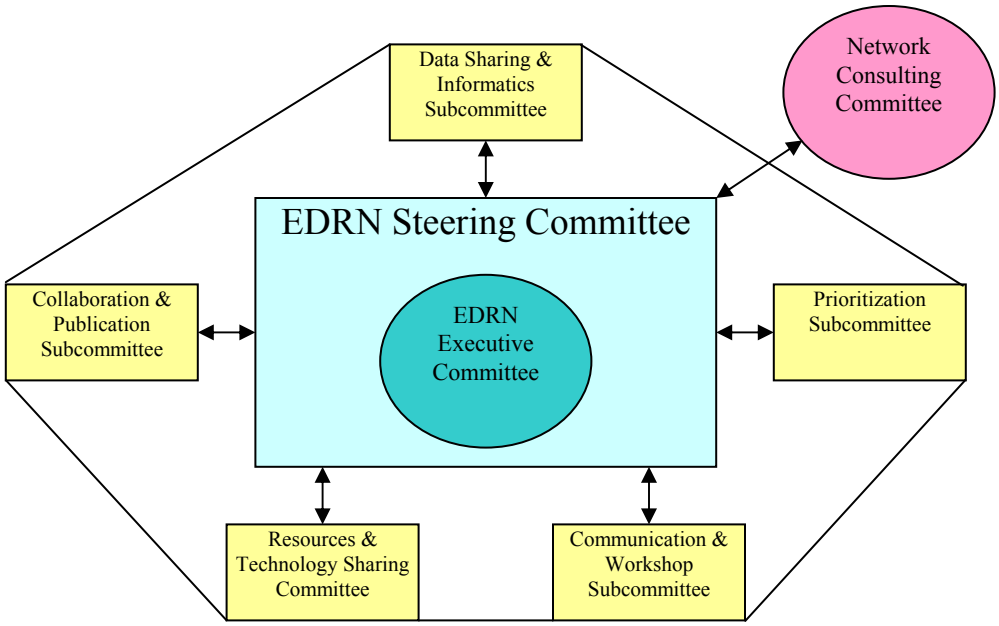
The operating procedures were initially approved January 2001 by the Steering Committee.

These procedures provide guidance for the administrative and operational activities of the EDRN and may be modified or revised by approval of the Steering Committee as experience and need dictates. Any member in good standing (i.e., a member who attends at least one Steering Committee meeting per year) may propose amendments to the procedures.

1.1 Statement of Objectives

- To support and facilitate a broad spectrum of research activities that address early development and initial validation stages of molecular biology and genetics, including biomarkers that can be applied in risk prediction, early detection and primary prevention of cancer.
- To coordinate national and international research programs for the development of clinically useful biomarkers in preneoplastic lesions that accurately predict the risk of invasive cancer or the presence of early cancer in asymptomatic individuals not previously diagnosed with the disease.
- To support the development of databases on the utility of biomarkers and expression patterns that will serve as background information for larger validation and efficacy studies.
- To promote collaboration and communication with other programs at the NCI, other Institutes within NIH, organizations with the National Cancer Program, and academic and industrial leaders from relevant disciplines.

SECTION 2 COMMITTEES



2.1 Steering Committee

2.1.1 Overview

The Steering Committee (SC) has major scientific management oversight and responsibility for developing and implementing a collaborative Network research program including protocols, publications, and design. The Committee consists of a Chair, Co-Chair, the EDRN Principal Investigators or a designee, and the NCI Program Director or a designee. A Principal Investigator cannot designate an Associate Member to replace him/her at an SC meeting. Members of the SC review all data collected in Network studies, monitor study results, follow-up, and report to the full SC upon request of the Chair. Each member has one vote.

According to the requirements of the Cooperative Agreement, there are 2 SC business meetings, and one scientific workshop each year that EDRN members should attend. The time and site for these meetings are determined by SC members. The Principal Investigator from each Cooperative Agreement is required to attend at least one SC meeting each year. There must be at least one representative from each Cooperative Agreement, however, at every SC meeting. The minutes of the SC meetings are prepared by the DMCC as a matter of record and distributed to the members of the SC for approval at the next meeting. NCI reserves the right to terminate a grant for failure to attend or have representation at SC meetings.

2.1.2 Responsibilities and Privileges

- Develop guidelines for operating the EDRN
- Coordinate the research program within EDRN
- Develop criteria for reviewing progress of EDRN
- Establish and track milestones
- Develop and implement rules for sharing data and resources
- Disseminate information on the availability of resources (tissues, new technologies, and patients) within EDRN
- Develop criteria for selecting an Associate Member of the EDRN
- Develop criteria on the use of the Core Funds
- Develop and approve protocols for clinical research through the EDRN
- Develop criteria on evaluating and reviewing data on potentially promising new biomarkers
- Prepare annual Progress Reports for submission to NCI at the end of each fiscal year

2.1.3 Chair

The Chair and Co-Chair are elected by the full SC. Any member of the SC can offer nominations for the Chair and Co-Chair. The term of office for both the Chair and Co-Chair is two years with eligibility for re-election for one additional year. The Chair makes all appointments in consultation with the SC.

2.1.4 Duties of the Chair

- Preside at all meetings of the full SC
- Appoint and re-appoint members of Subcommittees, Review Groups, Working Groups, and designate special assignments
- Appoint the Chairs of Subcommittees, Review Groups, Working Groups, and Collaborative Groups
- Appoint ad-hoc committees as needed
- Invite consultants as needed to Subcommittees, etc.
- Appoint EDRN liaison members to other organizations
- Serve as a Co-Chair of the Executive Committee
- Serves as an ex-officio member of all Subcommittees, ad hoc Committees, and Task Forces
- Submit annual EDRN Progress Reports to NCI and the Network Consulting Committee
- Prepare the agenda for the SC meetings

2.1.5 Duties of the Co-Chair

- Serve as acting Chair during absence of the Chair
- Serve as chair of the Executive Committee

2.1.6 Quorum

For holding meetings, including conference calls, a quorum is defined as the presence of the majority of SC members. If a quorum is not present, the meeting will be cancelled.

2.2 Executive Committee

2.2.1 Overview

The Executive Committee (EC) consists of a Chair, Chair of the SC, Chairs of Collaborative Groups, at least one Principal Investigator from a BDL, BVL, CEC, and DMCC (if not represented in the Collaborative Group Chairs), and the NCI Program Director or a designee. The Committee is chaired by the Co-chair of the SC. The EC meets as necessary to conduct the business of the EDRN or at the discretion of the Chair of the EC or SC. The minutes of the EC are prepared by the DMCC as a matter of record and distributed to the members of the EC for approval at the next meeting.

The Committee expedites the work of the SC and assists the Chair of the SC. It coordinates the administrative and research activities of the EDRN on a regular basis and provides a mechanism for communication on the management of the EDRN. The Committee makes recommendations on major policy issues to the SC.

2.2.2 Responsibilities and Privileges

- Facilitate the work of the SC and assist the Chair of the SC
- Coordinate the administrative and research activities of the EDRN on a regular basis and serve as a forum for communication on the management of EDRN
- Conduct routine business to consider distribution of funds and to review and recommend for approval all research proposals submitted to the SC
- Recommend the release of Restricted and Core Funds to NCI
- Act for the SC on administrative and scientific matters between the semiannual SC meetings
- Oversee responsibilities of the Collaborative Groups

2.2.3 Duties of the Chair

- Serve as Co-Chair of the SC
- Preside over meetings of the EC
- Prepare the agenda for EC meetings

2.2.4 Duties of the Co-Chair

- Serve as acting Chair during absence of the Chair
- Serve as chair of the Steering Committee

2.2.5 Quorum

For holding meetings, including conference calls, a quorum is defined as the presence of the majority of EC members. If a quorum is not present, the meeting or conference call will be cancelled.

2.3 Network Consulting Committee

2.3.1 Overview

The Network Consulting Committee (NCC) is independent of the programmatic oversight provided by the NCI. The NCC is a non-voting committee, composed of non-federal scientists, clinicians, patient advocates, and ethicists who are devoid of financial and/or collaborative affiliation with EDRN where a conflict of interest exists or may be apparent. The Chair and members of the NCC are recommended by the EDRN SC and selected by the Chair, EDRN SC in consultation with NCI. At the recommendation of the NCI or Chair, EDRN SC, ad-hoc consultants may be recommended to serve on the NCC. Ad hoc consultants may be called upon for consultation in areas where specific expertise is needed yet lacking in the NCC. Ad hoc consultants may be federal or non-federal scientists, clinicians, patient advocates, and ethicists.

2.3.2 Responsibilities and Privileges

The primary role of the NCC is to assist the NCI and EDRN in evaluating the overall Network concept. The NCC will assist in the evaluation and operation of the EDRN by:

- Exchanging facts, materials, or information pertaining to the review of progress and planning of research within the EDRN
- Providing non-binding advice of individual members (not consensus advice or consensus recommendations) to the EDRN SC or EC, when appropriate
- Reviewing the progress of the EDRN, which may include a member's participation in site visits
- Considering new research initiatives to ensure the EDRN is responsive to promising opportunities in early cancer detection research and risk assessment
- Serving as members on ad-hoc committees of the EDRN, including Review Groups, Working Groups and Collaborative Groups, and as Consultants to Subcommittees
- Assisting the EDRN SC in planning and organizing workshops and symposia
- Participating in EDRN workshops and symposia
- Serving as a liaison between the cancer research community and the EDRN

- Meeting with NCI and EDRN leadership at the request of the Chair, NCC, NCI, or Chair, EDRN SC

2.3.3 Chair

Appointed by the Chair, EDRN SC in consultation with the NCI for an unspecified term.

2.3.4 Duties of the Chair

- Presides over all meetings of the full NCC
- Serves as liaison with NCI Program Director or designee

SECTION 3 SUBCOMMITTEES

3.1 Overview

Subcommittees are the policy-making working groups of the EDRN and report to the SC when requested by the Chair. Subcommittees meet twice a year in conjunction with the SC business meetings. Conference calls are made any time on the recommendation of the Chair of either the SC or Subcommittees. Formal meetings between the semiannual meetings require approval by the Chair of the SC.

Voting members of the Subcommittees are the members of the SC, that is the Principal Investigators in the EDRN. Co-investigators, Associate Members, and other interested parties, however, are welcome to attend Subcommittee meetings as consultants. The Chair of the SC appoints members to the Subcommittees, although SC members can express their preferences on which Subcommittee they would like to serve. Members cannot serve on more than one Subcommittee simultaneously. Members are appointed for two years and can be re-appointed for a second, two-year term. Each Subcommittee member has one vote. Consultants for Subcommittees can be appointed by the Chair of the SC or by the Chairs of the Subcommittees as non-voting members.

3.1.1 Chairs

The Subcommittee Chairs are appointed by the Chair of the SC. A Chair may be a Principal Investigator or a co-Principal Investigator of EDRN. Term of office is two years. It is the duty of the Subcommittee Chairs to determine whether a quorum is present before opening the meeting. The Chair has the responsibility to prepare the agenda and to report to the Steering Committee.

3.1.2 Quorum

A quorum for all Subcommittee meetings, including conference calls, is defined as the presence of the majority of Subcommittee members. If a quorum is not present, the meeting or conference call will be cancelled.

3.2 Collaboration and Publication Subcommittee

3.2.1 Objective

The objective of the Collaboration and Publication Subcommittee is to define procedures and conditions for formal collaboration within the EDRN and with investigators outside the Network, and defines publication policies.

3.2.2 Responsibilities and Privileges

- Develop procedures for formal research collaboration within and outside the EDRN, including collaboration with individual investigators, industry, academic centers, community hospitals, government agencies, international investigators, and Cooperative Groups
- Determine collaborative relation with private industry, especially with regard to IP issues
- Develop procedures for collaborating with NCI Programs, such as SPORE, CGAP and the Cancer Family Registries
- Determine the role of the SC in monitoring collaborative research within and outside EDRN
- Develop guidelines for order of authors, standard credits, statement for source of support, and common formats for the publication of EDRN research
- Assist in developing common EDRN materials needed for obtaining approval for EDRN studies from Institutional Review Boards

3.3 Technology and Resource Sharing Subcommittee

3.3.1 Objective

The objective of the Technology and Resource Sharing Subcommittee is to establish the rationale and conditions for sharing technology and other resources among investigators within and external to the EDRN.

3.3.2 Responsibilities and Privileges

- Develop guidelines for sharing novel technology, reagents, and resources within the EDRN
- Develop guidelines for external Network sharing
- Develop guidelines and responsibilities for considering IP issues

3.4 Communication and Workshop Subcommittee

3.4.1 Objective

The objective of the Communication and Workshop Subcommittee is to achieve the full potential of biomarkers as tools to facilitate early detection of cancer by disseminating research goals and findings with the broader components of the research enterprise. To accomplish this objective, the Communication and Workshop Subcommittee defines formats for exchange of scientific findings such as workshops, seminars, and electronic information resources that serve to inform the research communities of scientific advances.

3.4.2 Responsibilities and Privileges

- Develop long-term strategies that facilitate the translation of research advances into screening and detection practices
- Identify mechanisms to extend biomarker research to enable commercial development of diagnostic tools through public-private partnerships or collaborations
- Interact with organizations that facilitate the use of biomarkers in the clinical arena and discuss the long-term implications of biomarkers as screening and detection tools in population health
- Identify key audiences to engage/inform about EDRN research activities, goals, etc.
- Communicate with oncology groups, cancer research societies, immunology, biochemistry, pathology groups, epidemiology and biostatistical communities, biotechnology/bioengineering developers; technology transfer offices, voluntary health organizations, public health organizations, managers of health care, and regulatory agencies, etc.
- Organize workshops to inform other components of the research community of the opportunities and needs to implement biomarkers in clinical screening, clinical trials, and early detection, etc.
- Develop other communication mechanisms to facilitate information dissemination (e.g., electronic media (websites, listservs) for communication among centers, data registries, newsletters, supplements to journals).
- Oversee liaisons
- Assist in developing common EDRN materials needed for obtaining approval for EDRN studies from Institutional Review Boards

3.5 Prioritization Subcommittee

3.5.1 Objective

The objective of the Prioritization Subcommittee is to establish procedures for prioritizing research and allocating resources within the Network.

3.5.2 Responsibilities and Privileges

- Define the decision criteria needed for the evaluation of biomarkers beyond the discovery stage and set up a review process for implementing them in the EDRN
- Develop guidelines for coordinating the prioritized projects across the Network including obtaining involvement of the NCC
- Establish guidelines for utilization of the Core Funds and allocation of research resources
- Ensure integration of various components of the EDRN with the NCI Bypass Budget

- Develop metrics for evaluating the progress (success) of EDRN. Establish annual and overall milestones for EDRN that will be used for evaluating Network progress and reporting to the NCC, NCI Executive Committee, NCI Board of Scientific Advisors, and National Cancer Advisory Board

3.6 Data Sharing and Informatics Subcommittee

3.6.1 Objective

The objectives of the Data Sharing and Informatics Subcommittee are to establish guidelines for the EDRN data structure and common data items, and to provide a forum for biostatisticians/analysts within EDRN to collaborate on research pertinent to EDRN.

3.6.2 Responsibilities and Privileges

- Develop EDRN Informatics Enterprise System compatible with NCI Informatics Enterprise, NCI standards, and CTEP systems and evaluate for EDRN members
- Develop guidelines for security levels of the centralized database
- Develop guidelines for internal and external data sharing that include mechanisms to ensure that the data are used appropriately
- Develop guidelines for statistical design and evaluation of biomarkers
- Develop guidelines for posting materials on the secure website
- Review patient privacy requirements for EDRN in conjunction with the relevant Subcommittee
- Develop methods to promote data sharing with NCI programs such as CGAP, CGN, SEER, etc.

SECTION 4 GROUPS

4.1 Standing Review Group

The Standing Review Group is responsible for reviewing Associate Membership applications and proposals requesting use of Core Funds, including validation proposals. Members are nominated by the Chairs of the Collaborative Groups and the Prioritization Subcommittee and appointed by the Chair of the SC. The Group consists of one Principal Investigator from a BDL, one Principal Investigator from a CEC, one Principal Investigator from a BVL, the Principal Investigator or designee from the DMCC, and two members from the Prioritization Subcommittee. Additional EDRN and non-EDRN consultants can be added at the discretion of the EC. Details on the application and review processes are under the 'Policies and Procedures' section of this manual.

4.2 Working Groups

Working Groups shall be created for specific, finite projects as deemed needed by the SC or EC. Members to Working Groups are appointed by the Chair of the SC.

SECTION 5 ACTIVITIES TO PROMOTE COLLABORATION

5.1 Collaborative Groups

Collaborative Groups are organ-specific groups designed to promote the exchange of information on organ related biomarkers and identify research priorities within EDRN. Members of the Collaborative Groups are the members of the SC, their co-investigators, Associate Members, and other interested parties. Members are encouraged to participate on the Collaborative Group that best reflects the expertise presented in their original peer-reviewed application. Members cannot serve on more than one Collaborative Group simultaneously. There are four Collaborative Groups: Breast/Gynecology, Prostate and Urologic, Lung and Upper Aerodigestive Tract, and G.I. and Other Associated Cancers. Please see Appendix III for Collaborative Group rosters.

5.1.1 Chairs

The Collaborative Group Chairs are appointed by the Chair of the SC. A Chair must be an EDRN Principal Investigator. Term of office is two years. It is the duty of the Collaborative Group Chairs to determine whether a quorum is present before opening the meeting. The Chair has the responsibility to prepare the agenda and to report to the Steering Committee.

5.1.2 Quorum

A quorum for all Collaborative Group meetings, including conference calls, is defined as the presence of the majority of members. If a quorum is not present, the meeting or conference call will be cancelled.

5.2 Liaison Members

The purpose of liaison members is to ensure that members of key scientific organizations are aware of EDRN activities and to ensure that EDRN members are aware of activities of outside organizations that may impact EDRN. Liaison members to scientific and professional organizations, including scientific programs at NCI, are appointed by the Chair of the SC. Liaisons are appointed to two-year terms with eligibility for reappointment for another two-year term. Liaison members report to the SC on activities by other organizations that are relevant to the EDRN during the semiannual SC meetings.

5.3 Sponsor

Act as spokesperson for the Associate Membership.

SECTION 6 POLICIES AND PROCEDURES

6.1 Associate Membership

The Associate Membership is designed for investigators who are not affiliated with EDRN and wish to propose collaborative studies within the scope and objectives of the EDRN. There are three categories for Associate Membership.

Category A Members are domestic or foreign investigators who propose to conduct basic or translational research consistent with the priorities of the EDRN. Supplemental funds provided through Category A Membership are to be used as one-time "seed money" for pilot studies necessary to support applications for future independent funding. Funds are provided for a period of one year and are not renewable. Although support of Category A Members ceases after one year, they are considered to be Associate Members for the duration of the EDRN. Category A Associate Members are invited to participate in Workshops and Steering Committee meetings. The "seed money" will be $50,000 per year for two years and the applicant has to write the budget in a way that he/she can attend one meeting per year.

Category B Members contribute to the Network by sharing available technologies, contributing specimens, making available high-risk registries and cohorts, and providing other resources complementary to the Network. They can be domestic or foreign. Category B Members can reapply for funds annually (funding amount should not exceed $100,000). Category B Members are considered Associate Members after funding ceases for the duration of the EDRN. Category B Associate Members are invited to participate in Workshops and Steering Committee meetings.

Category C, Corresponding Members, are scientists, organizations, clinicians, patient advocates, or ethicists who are interested in participating in Collaborative Group meetings and EDRN Workshops and Conferences yet do not receive funds from the EDRN. Category C Members will be invited to these meetings and conferences, but their expenses will not be supported by the EDRN. Category C members can be domestic or foreign. The application for Category C Members is the similar to that of other Associate Member applicants, with minor modifications: the budgetary document can be disregarded, and the proposal should explain how the applicant’s participation at the meetings and workshops will contribute to the mission of EDRN. Category C Members are considered Corresponding Members for the duration of the EDRN.

Associate Members are welcome to join a Collaborative Group on the basis of their expertise and interest. To apply for an Associate Membership, an applicant must be sponsored by an EDRN Principal Investigator. For details on the application procedure please see the EDRN website: http://edrn.nci.nih.gov/index.html.

6.1.1 Responsibilities of the Sponsor

Sponsors of Associate Members are responsible for submitting the initial membership application, representing their interests in SC meetings, and inviting them to EDRN meetings.

6.2 Funds

6.2.1 Definitions

There are two sources of funds available through EDRN: Restricted Funds and Steering Committee Core Funds. Restricted Funds are funds that are set aside from the annual budget of BDLs and CECs for Network Collaborative Studies. Investigators from BDLs must set aside 10% of their annual budget after the first year for Network Collaborative Studies. Investigators from CECs must set aside 15% of their annual budget for subject accrual after the first year for Network collaborative studies. The reimbursement will be based on the complexity and amount of clinical data, specimen types, duration of follow-up, and other factors within collaborative studies as decided by the Steering Committee. Applicants for the release of Restricted Funds must include their specific plans for responding to the terms and conditions section of their grant award notice. The use of these set aside funds is restricted and must be reviewed and approved by the EC and then recommended to, and approved by the NCI before release from the individual U01 awards.

Steering Committee Core Funds are reserved for post-award collaborative Network research and for expanding participation within the Consortium. These funds can also be used to assist in moving a marker through the validation process. Examples of validation funding needs include accrual of patients, scaling-up of reagents, contracting to other laboratories or companies to scale-up production and maintain the quality of reagents. Funds can also be used for data management, travel, meetings, and other collaborative activities of the Network.

6.2.2 Release and Use of Restricted Funds

A Principal Investigator may only apply for the Restricted Funds within his/her Cooperative Agreement award. Restricted Funds may only be used for projects that complement the scope of the Cooperative Agreement award. More than one investigator may request the release of Restricted Funds for one collaborative project. A Principal Investigator may apply for more than one year's Restricted Funds, however, a status report must be submitted to NCI and should specifically detail how the Restricted Funds were used before subsequent year funds are considered for release. The status report may be submitted as part of the annual progress report submitted by the Principal Investigator. The applications for the release of Restricted Funds are reviewed by the EC at their monthly meetings.

6.2.3 Application Requirements for Release of Restricted Funds

The application for release of Restricted Funds includes the EDRN Study Proposal Application Form and a proposal. The proposal must be single-spaced and follow NIH Format, as used in PHS Form 398. It should be organized and submitted as follows:

1. Title Page (page 1 of the PHS Form 398). Description (Abstract), Performance Sites, and Key Personnel (use page 2 of the PHS Form 398). Bibliography of key researchers involved (use page 6 of PHS Form 398).

2. Scientific Proposal and References (up to 5 pages), organized into Rationale, Goals, Sample Size, Preliminary Data (optional), Technologic Design and Approaches, Contribution to Translational Research, and EDRN Specific Aims/Deliverables. Address review criteria as established by the EDRN Steering Committee (see Review Criteria section below).
3. Budget Page - (final page unless an Appendix section is included). Use page 4 of the PHS Form 398. Adequate budget justification for direct costs is required.
4. Appendix (optional).
5. Ten paper copies and one electronic copy of the proposal should be submitted to the NCI EDRN Program Office.

All projects must comply with institutional regulations on research involving human subjects, children, minority groups, gender, animals, recombinant DNA, and hazardous materials. Appropriate approvals from the relevant committees, including approval from institutional review boards, must be submitted to the NCI EDRN Program Office before funds can be provided for successful applications.

6.2.4 Review Criteria

Review criteria are based on scientific merit and compatibility with EDRN objectives. Seven formal criteria are used to assess the suitability of proposals for supplemental support and/or advancement to the large-scale validation phase:

- Scientific merit
- Study design: e.g., prospective versus cross-sectional
- Technical parameters: reproducibility, sensitivity, specificity, throughput, automation, and cost
- Clinical or scientific impact: e.g., more common cancers or a significant impact in less common neoplasia
- Portfolio balance within EDRN
- Practicality and feasibility: e.g., required sample size, amount of tissue
- Collaborative strength, including contribution of resources and technology. Collaboration is a central mission of EDRN.

A project does not have to be strong in all review categories to be considered highly meritorious. For example, a methodology or infrastructure-related application may not be judged to be at a high level of scientific merit yet may be a critical component in an overall plan to achieve EDRN goals and may represent a high level of cooperation and interaction among investigators toward EDRN objectives.

6.2.5 Application Requirements for Release of Core Funds

Requests for Core Funds can be made by applicants for Associate Membership as well as EDRN investigators to conduct collaborative projects involving and focusing on EDRN

objectives or to advance current projects toward validation. Applicants may apply for only direct costs in support of the proposed research. Budgets must not exceed $100,000 unless sufficient justification is provided. Proposed budgets will be reviewed in $25,000 increments, consistent with the NIH modular grant application concept. Adequate budgetary information should be provided to justify proposed spending. Requests for supplemental funds are accepted on March1, July 1, and November 1. Applications not received by the receipt date are held until the following scheduled review.

EDRN investigators applying for funds to conduct collaborative projects must complete both the EDRN Study Proposal Application Form and a proposal following the format of PHS Form 398 as described in Section 6.2.3. Applicants for Associate Membership need only submit a proposal following the format of PHS Form 398 (see Section 6.2.3). All projects must comply with institutional regulations on research involving human subjects, children, minority groups, gender, animals, recombinant DNA, and hazardous materials. Appropriate approvals from the relevant committees, including approval from Institutional Review Boards, must be submitted to the NCI EDRN Program Office before funds can be provided.

6.2.6 Review Process for Applications for Release of Core Funds

The EDRN Review Group will review all Associate Membership applications and collaborative EDRN projects (excluding Validation Proposals) that seek Core Funds from EDRN. The EDRN EC will perform an accelerated review of applications for Associate Membership that do not seek funds from EDRN. The EC will review Validation Proposals that seek Core Funds or it will appoint an ad hoc committee that will include at least one member from the appropriate Collaborative Group. The specific criteria used to evaluate proposals are listed in the section above, Section 6.2.4. The review process is described below*:*

1. Copies of proposals received by the receipt date are forwarded from the NCI EDRN Program Office to the members of the EDRN Review Group within a week after the application receipt date.
2. The EDRN Review Group evaluates and scores applications and sends results to the NCI EDRN Program Office. The evaluation is expected to be complete by ten business days following the application receipt date. After evaluation, the NCI EDRN Program Office forwards the evaluation results to the Executive Committee.
3. The Executive Committee renders final approval of the reviewed proposals, informs the Steering Committee of successful applications, and submits the recommendations to the NCI EDRN Program Office. All of these actions are expected to occur within two months after the application receipt date.
4. The EDRN Chair's institution contacts NCI Grants Administration Branch by letter, requesting approval to release the restricted funds. Once the NCI Grants Administration Branch receives all approvals, NCI authorizes the release of funds.

6.2.7 Additional Information for Validation Study Proposals

Progress of a biomarker to a validation study is a critical step in the development of a biomarker and is, therefore, a critical part of EDRN. Due to the importance of the step and the fact that funding needs are likely to be large, the application process has some additional requirements to those of Associate Members. The differences are described below:

1. **Pre-proposal:**

   A pre-proposal/letter-of-intent, limited to 3 pages, must be submitted to the NCI EDRN Program Office. Validation Studies are collaborative, therefore, the pre-proposal must name the EDRN sites which will be included as part of the collaboration. A Biomarker Validation Lab and the Data Management and Coordinating Center must be included in all Validation Studies. A Clinical/Epidemiology Center should be included as needed.

   The Executive Committee (EC) reviews validation study pre-proposals monthly. Submissions received by the NCI EDRN Program Office by the first of the month are reviewed that month. Proposals not received by the first of the month are reviewed in the following month.

2. **Proposal:**

   Once the pre-proposal is approved by the EC, the investigator contacts a Biomarker Validation Lab, Data Management and Coordinating Center, and/or Clinical/Epidemiology Center, as appropriate for collaboration, and develops a full proposal with them. The full proposal should be prepared as described in Section 6.2.3 with the exception that it should not exceed 10 pages rather than 5 pages. A detailed background and rationale are not necessary but presentation of preliminary data is required.

   As with Validation Study pre-proposals, full proposals are reviewed monthly. Submissions received by the NCI EDRN Program Office by the first of the month are reviewed that month by the EC or appointed ad hoc committee. The remaining steps for the validation study review process are the same as steps 2-4 under Section 6.2.6, above.

6.3 Access to Secure Website

6.3.1 Website Overview

The Data Management and Coordinating Center (DMCC) is responsible for developing and maintaining a secure website for EDRN. The website contains general EDRN information such as contact information for all participating institutions, committee and subcommittee membership, upcoming events, etc., as well as items that are less public such as data from collaborative studies, approved validation proposals, paper drafts, etc. Due to the sensitive nature of some of the information available on the secure website, only people approved by an EDRN member have access to the website. Access to the website requires a log-in and password distributed by the DMCC.

6.3.2 Obtaining a Log-in and Password

In order to obtain access to the secure website, one must complete the Application for EDRN Secure Web Site Access (see http://www.compass.fhcrc.org/enterEDRN/) and fax the completed form to Marcy Winget (206-667-5964) at the DMCC. The application form must be signed by an EDRN Principal Investigator. Once the application is processed at the DMCC, the applicant is sent a log-in via email and a password via post mail. The log-in name generally consists of the applicant's first name initial and entire last name.

6.3.3 Passwords and Security Issues

Once an applicant receives their password, the DMCC recommends changing the password immediately. A user can change their password at any time by clicking on "Change Password" at the bottom of any page on the website. For security reasons, passwords for the EDRN secure website must be at least 8 characters long; the DMCC recommends using a combination of alphabetical and numeric characters. The DMCC also recommends that public personal data (e.g. name, birthday) should not be used in passwords. Log-in IDs and passwords should also be kept in a safe place. To maintain compliance with the DMCC's IRB, you may not share your password or log-in.

Each user's password will expire every four months. If a person enters his/her log-in and the password has expired, s/he is prompted to change the password at that time. A log-in will lock after three failed attempts and then reset itself in 30 minutes. If this happens, please wait 30 minutes and then try to log into the web site again.

APPENDIX I PARTICIPATING INSTITUTIONS AND MEMBERS

Brigham & Women's Hospital
Daniel Cramer, M.D., Sc.D.

Creighton University
Henry Lynch, M.D.

Duke University Medical Center
Jeffrey P. Marks, Ph.D.

Eastern Virginia Medical School
John Semmes, Ph.D.

Fred Hutchinson Cancer Research Center
Ziding Feng, Ph.D.

Genetica, Inc.
David Beach, Ph.D.

Georgetown University
Bruce Trock, Ph.D.

H. Lee Moffitt Cancer Center & Research Inst.
Melvyn Tockman, M.D., Ph.D.

Johns Hopkins University
Kathy J. Helzlsouer, M.D.

Johns Hopkins University
Alan W. Partin, M.D., Ph.D.

Johns Hopkins University
David Sidransky, M.D.

MD Anderson Cancer Center
Bogdan Czerniak, M.D., Ph.D.

MD Anderson Cancer Center
Margaret R. Spitz, M.D., M.P.H.

UT Southwestern Medical Center
Yingming Zhao, Ph.D.

National Center Infectious Diseases
Elizabeth Unger, M.D., Ph.D.

National Institute of Standards and Technology
Peter Barker, Ph.D.

Northwestern University
David Fishman, M.D.

NYU School of Medicine
William Rom, M.D., MPH

Thomas Jefferson University
Timothy Block, Ph.D.

University of Alabama at Birmingham
William Grizzle, M.D., Ph.D.

University of California, Los Angeles
David Chia, Ph.D.

University of Colorado Health Science Ctr.
Wilbur Franklin, M.D.

University of Maryland
Edward Highsmith, Jr., Ph.D.

University of Maryland
Stephen Meltzer, M.D.

University of Michigan
Dean Brenner, M.D.

University of Michigan
Samir Hanash, M.D., Ph.D.

Univerisity of Pittsburgh Cancer Institute
William L. Bigbee, Ph.D.

University of Texas
Ian Thompson, M.D.

University of Washington
Nancy Kiviat, M.D.

UT Southwestern Medical Center
Adi Gazdar, M.D.

Yale School of Medicine
Jose Costa, M.D.

APPENDIX II SUBCOMMITTEE MEMBERSHIP ROSTERS

Collaboration and Publication Subcommittee

	Appointment	Termination
Chair: Dr. David Fishman	2002	2004
Dr. Dean Brenner	2002	2004
Dr. Edward Highsmith	2002	2004
Dr. Nancy Kiviat	2002	2004
Dr. Alan Partin	2002	2004
Dr. Bruce Trock	2002	2004
Consultants:		
Dr. Greg Downing	2002	2004

Technology and Resource Sharing Subcommittee

	Appointment	Termination
Chair: Dr. Jeffrey Marks	2002	2004
Dr. David Beach	2002	2004
Dr. Timothy Block	2002	2004
Dr. David Chia	2002	2004
Dr. Jose Costa	2002	2004
Dr. Elizabeth Unger	2002	2004
Dr. Yingming Zhao	2002	2004
Consultants:		
Dr. Enrique Dalmasso	2002	2004
Dr. L. Austin Doyle	2002	2004
Dr. Jerry Henslee	2002	2004
Dr. Mukesh Verma	2002	2004

Workshop and Communication Subcommittee

	Appointment	Termination
Chair: Dr. Patrice Watson	2002	2004
Dr. Bogdan Czerniak	2002	2004
Dr. Kathy Helzlsouer	2002	2004
Dr. William Rom	2002	2004
Dr. John Semmes	2002	2004
Consultants:		
Ms. Michelle Busch	2002	2004
Dr. Donald Henson	2002	2004
Dr. Marcy Winget	2002	2004

Prioritization Subcommittee

	Appointment	Termination
Chair: Dr. William Bigbee	2002	2004
Dr. Ziding Feng	2002	2004
Dr. Wilbur Franklin	2002	2004
Dr. Adi Gazdar	2002	2004
Dr. Samir Hanash	2002	2004
Dr. Henry Lynch	2002	2004
Dr. Stephen Meltzer	2002	2004
Dr. Margaret Spitz	2002	2004
Dr. Ian Thompson	2002	2004
Consultants:		
Dr. Barnett Kramer	2002	2004
Dr. Sudhir Srivastava	2002	2004

Data Sharing and Informatics Subcommittee

	Appointment	Termination
Chair: Dr. Mark Thornquist	2002	2004
Dr. Peter Barker	2002	2004
Dr. Daniel Cramer	2002	2004
Dr. William Grizzle	2002	2004
Dr. Melvyn Tockman	2002	2004
Consultants:		
Ms. Heather Kincaid	2002	2004
Dr. Mukesh Verma	2002	2004
Dr. Wendy Wang	2002	2004
Ms. Denise Warzel	2002	2004
Dr. Dean Troyer	2002	2004
Dr. John Baron	2002	2004

APPENDIX III COLLABORATIVE GROUP ROSTERS

Breast and Gynecologic Cancers

Dan Cramer (Chair)
Peter Barker
Mary Benedetto
William Bigbee
David Euhus
David Fishman
Paula Friedman
Andra Frost
Lee Goodglick
Kathy Helzlsouer
Jerry Henslee
Barry Kacinski
Jeffrey Marks
Lisa Molz
Nancy Kiviat (Co-chair)
Carolyn Muller
Steven Skates
Timothy Stenzel
Paul Strickland
Mary Lou Thompson
Susan Tinley
Bruce Trock
Elizabeth Unger
Wendy Wang
Marcy Winget
Yingming Zhao
Tatyana Zhukov

G.I. and Other Associated Cancers

Dean Brenner (Chair)
William Anderson
John Baron
Robert Bresalier
Timothy Block
Bruce Boman
Jose Costa
Ziding Feng
Franca Formelli
William Grady
Donald Henson
Carrie Klabunde
Stephen Meltzer (Co-chair)
Henry Lynch
Upender Manne
Norman Marcon
Robert Schoen
Stuart Spechler
Sapna Syngal
Laura Steel
Yinghsui Su
Asad Umar
Wendy Wang
Patrice Watson

Lung and Upper Aerodigestive Cancers

Melvyn Tockman (Chair)
John Abraham
Doreen Addrizzo-Harris
Walter Bell
Ellen Eylers
Adi Gazdar
Sam Hanash
James Herman
Ed Highsmith
Lei Hong
Wilbur Franklin (Co-chair)
Catherine O'Connell
William Rom
David Sidransky
Jill Siegfried
Margaret R. Spitz
Mark Thornquist
Mukesh Verma
Denise Warzel

Prostate and Urologic Cancers

Ian Thompson (Chair)
David Beach
David Chia
Cathy Critchlow
Bogdan Czerniak
Enrique Dalmasso
William Grizzle
Betsy Higgins
John Semmes (Co-chair)
Jane Kuypers
Robin Leach
Scott A. Optenberg
Alan Partin
Lori Sokoll
Dean Troyer

APPENDIX IV EDRN PROGRAM EVALUATION

A. Metrics for Evaluation

A.1 Objectives

It is the responsibility of the awarding agency, in this case the National Cancer Institute (NCI), National Institutes of Health, to review progress achieved towards scientific goals in original grant applications over specified grant periods and to provide scientific and logistical input to grantees to enhance the quality of their scientific efforts. For details, see HHS 45 CFR, Part 74. To review progress towards achieving the objectives of the Early Detection Research Network (EDRN) and its investigators, it is imperative for EDRN program officials to gather information on the functioning of the network in order to update the NCI leadership. This document describes metrics, rationale, and standards for evaluating the overall success of the EDRN.

A.2 Introduction

Fair, rigorous peer review of investigator-initiated scientific applications remains the cornerstone of scientific progress in the United States. Peer review has ensured that the best science is supported. The EDRN was initiated with this concept in mind. By selecting scientific collaborators for the EDRN on the basis of rigorous peer review and fully funding the best applications, the NCI has successfully obtained strong participation from the scientific community.

The EDRN represents a major pioneering effort in collaborative translational research. It departs from prior Cancer Cooperative Group models in many important ways - through empowering investigators by funding their Centers directly and by placing the burden of scientific leadership, research agenda, and collaboration upon these directly funded Centers. Basic scientists with robust bench research records have been funded to pool their ideas, resources, and tools. Translational and epidemiologic investigators with strong tools and publication track records are directly funded with a mandate to translate concepts arising from basic science labs. Analytical tools, laboratories, statistical methods, and informatics are also supported directly with a collaborative mandate. Leadership of this collaborative must emanate from the grass-root investigators, and the Executive Leadership must communicate with a highly knowledgeable group of scientists in a manner that enhances collaboration and productivity. This Network represents a new paradigm of Cooperative research.

A.3 NCI Charge to the EDRN

At the opening meeting of all of the funded EDRN units, NCI leadership and Program Staff provided the following charge for this collaborative enterprise:

- Establish criteria for the discovery and validation of biomarkers at all points of the integrated research scheme;
- Establish a rigorous quality assurance/quality control program for biomarkers;

- Establish and deal with issues of biorepositories -- how the samples will be obtained, stored and most importantly, allocated;
- Support Translational Research Projects-both within and outside the EDRN - and establish policies and procedures that are inclusive of investigators who wish to utilize the infrastructure and facilities of the EDRN;
- Establish and foster industrial collaborations which will be crucial to the ability to rapidly translate the research effort into products and to test innovative biomarkers being developed by industry;
- Establish and maintain effective and efficient communications, including the use of EDRN websites (public and private), listservs, email, and regularly scheduled meetings;
- Develop and maintain an effective, efficient, and productive management domain with minimal committee structure and maximal collaboration, with financial rewards for collaboration;
- Encourage inclusiveness by ensuring that scientists with promising research ideas get the opportunity to collaborate constructively with the EDRN.

B. Evaluation Metrics

Since there are no prior models of such a cooperative research enterprise, it is very important to carefully monitor and assess progress from both macro and micro perspectives. This review will be particularly important during the first grant period in which substantial administrative effort should be expended in order to build the new infrastructure. The following evaluation metrics are suggested.

B.1 For the Individual Laboratory and Center

3. Scientific Excellence

   Quality of Questions: Has the EDRN site clearly defined their objectives, hypotheses, and scientific plan?

   Scientific Progress to Date: Has the EDRN site made progress towards meeting these objectives as specified in their originally funded research plan? What pitfalls have been encountered and how have they been managed?

   Innovation: How has the EDRN site used innovation to overcome obstacles? Is the site aware of new methods or approaches that might be useful to or portable into the EDRN environment?

   Future Plans: What does the site plan to do over the coming two years? How will these plans meet the original grant objectives?

4. Productivity Metrics

   Publication productivity: Has the site published papers on the objectives funded by the EDRN? How many and in what Journals? If not, are there problems that need to be addressed or require assistance?

Grant funding: Has the site applied for additional grant or contract funding? Has the site team been successful in gaining additional funds? Has the EDRN been helpful to the success of funding these new grants or contracts?

Biomarkers identified (BDLs): Number of new biomarkers pursued for evaluation? Number of biomarkers sent forward to CECs or BVLs for validation? Number of biomarkers added to early detection or risk assessment panels? Number of biomarkers used in chemoprevention clinical trials?

Assays performed (BVLs): Numbers of assays developed for EDRN projects? Numbers of samples processed? Types of samples processed? Results reported? Quality control of samples assayed? Number and type of development projects approved? Use of CDEs?

DMCC: Standards of informatics support? Type of informatics, QC procedures, patient privacy protection measures, data storage, and retrieval systems for Validation Studies? Development of Network-wide communication systems? Development of Network-wide systems to promote data and specimen sharing? Development of statistical methodology to meet the needs of EDRN?

Samples collected and provided (CECs): Numbers of samples collected? Types of samples collected? Sources of samples collected? Numbers of samples provided to EDRN BDLs or BVLs? Use of CDEs? How many CECs have had their set-aside funds released? How many CECs have requested the release of Developmental funds?

5. Collaborative Metrics

EDRN collaborations: With whom is the EDRN site collaborating? How many projects are collaborative? How many joint papers have been published? Use of EDRN resources: Has the EDRN site collaborated with CECs, a BVL or BDL site? If so, how many? Joint publications? Joint grants? How many BDLs have requested release of their restricted funds for Network Collaborative Studies?

Participation in EDRN Activities: Attendance from the site at EDRN meetings. Participation on Committees, working groups, and task forces? Special EDRN projects completed. Did EDRN site participate in developing the CDEs? Did EDRN site help to standardize/streamline the IRB approval process? Did EDRN site help develop systems for streamlining data sharing and/or specimen sharing? Did EDRN site help develop systems to standardize/streamline technology transfer issues?

EDRN outreach: Number of new Associate Members from the outside? Amount of Chair's funds allocated to new Associate Members? The number of applications for Chair's funding? Other outreach activities?

B.2 Process for Evaluating Metrics

6. Annual written progress report

Reviews should be based upon the yearly progress report required for non-competitive renewal. Instructions for preparation of the non-competitive renewal should be specific and emphasize progress towards scientific goals of the original grant application and

progress towards addressing EDRN's mission. While scientific quality and progress need to be recorded and addressed, primarily, metrics should be required to allow NCI staff to report data to NCI leadership.

The review process should assess the progress of each of the funded units towards meeting the specific aims of their funded grant application and their progress and contributions in meeting the above-described charges for the entire group. While the review is structured to provide NCI leadership and staff with data to track the progress of the EDRN and its components, equally important goals are to provide constructive feedback to EDRN Principal Investigators and their collaborators. Reviews may be used by EDRN leadership, NCI staff, and the Network Consulting Committee to make mid-course changes or to encourage constructive changes in individual scientific direction or focus. Initial reviews might assist in building collaborations among investigators and their groups. Reviews may also be used to assess administrative progress, to quantify publications and grants, and to quantify numbers of subjects studied.

7. Site Visits:

   Each Center/Laboratory should be site visited by a panel comprised of external consultants (individual members of the Network Consulting Committee), NCI staff and other experts on an as needed basis. The site visit should be brief (preferably a half day or less) but enable a thorough review of scientific progress, future scientific plans, performance metrics, facilities and staff in support of the EDRN charge. The site Principal Investigator would provide a 2-3 hour presentation period to review scientific progress, spell out new scientific initiatives for EDRN research, and address required metrics. The Principal Investigator should be encouraged to share problems, concerns, and questions to the site visit team so that the process is interactive and collegial. While an agenda and presentation should be necessary, no scoring should be used.

8. Frequency of Site Visits

   The frequency of the site visits will be determined by the NCI. However, it is anticipated that one initial site visit by NCI program officials, in year one will occur, and one mid-grant site visit (for a five-year grant, it will be the between the year 2 and year 3). Additional site visits may be required when deemed necessary by the NCI.

   Deficient performance and remedies will be conducted in accordance with HHS 45 CFR, Part 74 and other pertinent regulations.

C. Overall Evaluation of Early Detection Research Network

It is the intention of the NCI that the members of the Network Consulting Committee and Chairs and Co-Chairs of the EDRN Steering Committee will discuss the overall performance of the EDRN using the metrics presented in this document and suggest changes/modifications in the working structure of EDRN for the next five-year cycle.

Cancer Center Review Model: Perhaps the best model to evaluate the success of the EDRN is a Cancer Center type review. View the EDRN as a "Cancer Center" that is devoted to discovery and translation of surrogate endpoints for early cancer detection and risk assessment. In a Cancer Center review, the Center's leadership and Program Directors are

asked to demonstrate how the sum exceeds the total of its parts. This approach requires all program leaders, participating investigators, and Center leadership to demonstrate how the Core facilities, administration of resources, and Core grant funding have enhanced scientific progress. This review measures collaborative efficacy.